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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/413,110	10/06/1999	EVAN C. UNGER	UNGR-1580	1596

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DAVID A CHERRY ESQ
WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
ONE LIBERTY PLACE 46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER	
SHARAREH, SHAHNAM J	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/413,110	UNGER, EVAN C.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *116-184* is/are pending in the application.

4a) Of the above claim(s) *132-137, 142-145, 152-159, 161-163, 167 and 175-177* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *116-131, 138-141, 146-151, 160, 164-166, 168-174 and 178-184* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 08, 2004 has been entered.

Claims 116-184 are pending. This Application contains claims 132-137, 142-145, 152-159, 161-163, 167, 175-177 drawn to nonelected species. Claims 116-131, 138-141, 146-151, 160,164-166, 168-174, and 178-184 read on the elected species and have been acted on merits. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any rejection that is not addressed in this Office Action is considered obviated in view of the Amendment and the presented arguments.

Applicant's arguments with respect to the priority date of the instant application have been fully considered and are found persuasive. Accordingly, the effective priority date of this Application is June 19, 1996 because the parent application SN 08/666129, now Patent 6,033,645 has described effective ultrasonic energy for delivery of bioactive agents in col. 5, lines 28-29; col. 7, lines 37-49, and col. 41-42.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 116-131, 138-141, 146-151, 160,164, 168-174, and 178-184 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims of copending Application No. 09/218,660. The conflicting claims are still not patentably distinct from each other for the reasons of record.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Examiner notes Applicant's intention to file a terminal disclaimer once a favorable ruling is issued.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 116-131, 138-140, 160 are rejected under 35 U.S.C. 102(b) as being anticipated by Siegel US Patent 5,695,460.

Siegel discloses methods of utilizing an ultrasonic energy and an ultrasonic contrast agent containing perfluorinated microbubbles in combination with a thrombolytic agent to treat vascular thrombosis, (abstract; col 2 lines 1-65; examples 1-5; col 14, lines 4-30). Siegel specifically disclose that the ultrasound may be applied intravascularly by means of a miniature ultrasonic transducer or by a guide wire for transmitting ultrasound directly into the vessel (col 2, lines 7-10). Siegel's preferred ultrasound contrast agent is Echogen which contains phospholipids and polyethylene glycol (col 5, lines 50-53). Siegel et al further indicate the use of other types of contrast agents such as gas filled liposomes, or gas filled microbubble for their thrombus lysing method (col 5, lines 30-48). Siegel administers his drugs to an area in proximity of a thrombosis, which by its nature is hypo-perfused. Accordingly, Siegel et al meet the limitations set forth in the instant claims.

Applicant's arguments with respect to this rejection have been fully considered but are not found persuasive.

Applicant argues that Siegel does not teach delivery of bioactive agents through the vessel wall. See Arguments at page 15. Applicant further emphasizes that Siegel does not describe applying ultrasonic energy to increase delivery of a bioactive agent from the vasculature through the vessel walls and into selected tissues, because Siegel employs lower ultrasound frequencies in compare to the instant claims.

In response, Examiner states that during patent examination, the pending claims are "given the broadest reasonable interpretation consistent with the specification." MPEP 2111. Accordingly, given the broadest reasonable interpretation, the instant claims do not exclude the process of Siegel, because the instant ultrasonic energy sufficient to produce cavitation or rupture of vesicles leading to increase delivery of bioactive agent from vasculature through the vessel walls are inherent to the process of Siegel.

As the initial matter, the recitation of "increasing delivery of bioactive agents from the vasuclature" is viewed to be relative to an intravenous delivery process of a bioactive agent wherein no ultrasound energy is employed. Since Siegel employs at least some level of localized ultrasound energy, his process is deemed to increase delivery of a bioactive agent, because it has shown that at least in the case of thrombosis, bioactive agents are more effective when used in conjunction with a gaseous contrast agent and external ultrasound energy. Thus, at least this limitation is inherent to the process of Siegel.

Second, the recitation of "delivery of bioactive agent from the vasculature through the vessel wall" is inherent to methods of intravenous delivery in general. Applicant appears to be ignoring the fundamentals of blood vessel anatomy, and the absorption of endogenous molecules through blood vessel structure. In order to assert their clinical benefits, bioactive agents administered intravenously must go through the vessel walls. In another words, absorption occurs through the vasuclature structure. It is well established in the art that blood vessels are composed of three cellular layers, and at

least one of such layers, *Tunica Intima*, include endothelium cells that lines the lumen of all vessels. Such endothelium layer allows absorption of molecules through the vessel walls.[1] Therefore, such functional outcome is inherent to the process of administering drug intravenously.

Finally, pages 67-69 of the instant application, the recitation of therapeutic ultrasound is described. Nowhere does the specification exclude the ultrasound energy waves employed by Siegel as a type of energy that cannot increase drug absorption throught the vessel wall. More specially, at the bottom of page 68, the specification states:

> In therapeutic ultrasound, continuous wave ultrasound is used to deliver higher energy levels. For the rupture of vesicles, continuous wave ultrasound is preferred, although the sound energy may be pulsed also. If pulsed sound energy is used, the sound will generally Preferably, the echo train lengths are about 20 pulses at a time. **In addition, the frequency of the sound used may vary from about 0.025 to about 100 megahertz (MHz).** In general, frequency for therapeutic ultrasotmd preferably ranges between about 0.75 and about 3 Mllz, with from about 1 and about 2 MHZ being more preferred. In addition, energy lè vels may vary from about 0.5 Watt (W) per square centimeter (cm2) to about 5.0 W/cmz, with energy levels of âom about 0.5 to about 2.5 W/cm2 being preferred. Energy levels for therapeutic ultrasound involving hyperthermia are generally from about 5 W/cm2 to about 50 W/cmz. For very small vesicles, for example, vesicles having a diameter of less than about 0.5 jtm, higher frequencies of sound are generally preferred. This is because smaller vesicles may be capable of absorbing sonic energy more effectively at higher âequencies of sound. When very high frequencies are used, for example, greater than about 10 Ml-lzy the sonic energy may penetrate fluids and tissues to a limited depth only. Thus, external application of the sonic energy may be suitable for skin and other superficial tissues. However, it is generally necessary for deep

Since Siegel's energy waves falls within the 0.025-100 MHz range, it also is capable of providing therapeutic ultrasound within the meaning of the instantly claimed "ultrasonic energy in an amount sufficient to produce cavitation or rupture and sufficient to increase delivery of the bioactive agent from the vasculature through the vessel walls."

Further, the recitation that an element is "sufficient" or "capable" to perform a given function is not a positive limitation but only requires the ability to so perform. It

[1] See Absorption and distribution of Drugs, at pages 91-92 obtained from the website,

does not constitute a limitation in any patentable sense. *In re Hutchinson*, 69 USPQ 138. Accordingly, as the process steps of Siegel are the same as the instantly claimed methods, and the instantly claimed tissue encompasses vascular ischemic tissues; Siegel's delivery of thrombolytics to vascular ischemic tissues anticipates the limitations of the instant claims.

Thus, Siegel anticipates the limitations of the instant claims.

Claims 141, 146-151 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al US Patent 5,695,460.

Although Siegel does not specifically teach various infusion rates or various types of liposomal entities as the instant claimed invention, he does indicate the use of various types of contrast agents such as gaseous liposomes in this methods, accordingly, it would have been obvious to one of ordinary skill in the art to use a perfluorinated liposomal entity known in the art and further determine its suitable rate of infusion by routine experimentation, because he would have had a reasonable expectation to succeed in enhancing the lysis of a vessel thrombus when utilizing a gas filled liposomal contrast agents. Moreover, changes in rate of administration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such rate of administration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

~~druglibrary.org/schaffer/ library/studies/ledain~~, Last visited on June 10, 2004

Applicant argues that the instant methods are directed to delivering a bioactive agent through the vessel walls into selected tissues.

Again as reasoned above, Siegel's methodologies anticipate such limitations. Therefore, the mere failure of Siegel to recite such limitation verbatim does not impart patentability of the instant claims over the methods of Siegel.
methods are directed to a different purpose. In reply Examiner states that as discussed above, Siegel clearly teaches the method steps of the instant claims, accordingly, modifying the rate of infusion would have been achieved by routine experimentation.

Claims 116-131, 138-141, 146-151, 160,164-166, 168-174, and 178-184 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al US Patent 5,695,460 in view of Porter US Patent 5,648,098.

The teachings of Siegel are described above. Siegel doesn't teach the instant rate of administeration nor does he specifically recite higher ultrasound frequency limits of the instant claims 164.

Porter teaches the effective use of perfluorocarbonated microbubbles alone at a rate of 0.0025-1ml/kg over about 1-25 minutes (which is roughly about 1.6×10^{-6} to 6×10^{-6} ml-kg/sec), wherein perfluorocarbon gas is perfluorobutane (see claims 1-5) and wherein the microbubble concentration was less than 0.8×10^{9} or greater than $1.5\ 10^{9}$ per each milliliter (col 6, line33-36). Thus, allowing an artisan to accurately measure the dose of the microbubbles during the infusion. However, Porter fails in both of his teachings disclose vesicles comprising phospholipids.

Porter and Siegel are viewed as being in the same field of endeavor because they all teach the enhancement of thrombolytic activity when administering perfluorinated microbubbles.

Although Siegel does not teach specifically teach the optimal rate of administration or the ultrasound frequency of claim 164, one ordinary skilled in the art would have been motivated at the time of invention to use optimize such features as provided by general guidelines described in Porter. One of ordinary skill in the art would have had a reasonable expectation to succeed in optimizing the results, because as shown by Porter, rate of administration and availability of contrast agents improve the clinical outcome. Further, it is well within purview of an ordinary skilled artisan to optimize and determine the suitable rates for administration of the contrast agents that are disclosed by Porter.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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RUSSELL TRAVERS
PRIMARY EXAMINER
GROUP 1200